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J Crit Care 76 (2023) 154291

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Low dose vs high dose tocilizumab in COVID-19 patients with hypoxemic respiratory failure

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ARTICLE INFO

Keywords:
Immunosuppression
Interleukins
Medication therapy management
Respiratory infections
Respiratory failure
Corticosteroids

ABSTRACT

Purpose: Tocilizumab has been shown to decrease mortality when used concomitantly with steroids in COVID-19 with 8 mg/kg (max 800 mg) being the standard dose. Our study sought to assess whether a low dose (400 mg) shows similar benefit compared to a high dose for COVID patients concurrently on the same median dose of steroids.

Materials/Methods: A retrospective, multihospital observational study of COVID-19 patients who received tocilizumab in conjunction with steroids between March 2020 and August 2021 was conducted.

Results: A total of 407 patients were analyzed with low dose group being significantly more ill at baseline as a higher percentage of patients received vasopressors, were admitted to the ICU and on mechanical ventilation. In the propensity-matched analysis, both groups receiving a median dexamethasone equivalent dose of 10 mg showed no difference in 28-day mortality ($p = 0.613$). The high dose group had a higher rate of fungal and viral infections.

Conclusion: Compared to low dose tocilizumab, the high dose did not provide additional efficacy and mortality benefit but resulted in higher fungal and viral infections. This study illustrates that low dose tocilizumab can be an alternative to high dose during a drug shortage of tocilizumab without compensating for efficacy and safety, conserving resources for more patients.

1. Introduction

Hyperinflammatory response from SARS-CoV-2 infection can contribute to severe disease severity and even death in COVID-19 [1]. Decreasing inflammation has improved survival for patients with severe infection and hypoxemia from COVID-19 [2]. Various non-steroid immunomodulators were investigated for the treatment of COVID-19 targeting different aspects of the hyperinflammatory response. These include inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, both of which are associated with higher levels of viral replication, increased disease severity, and increased mortality [3,4]. Tocilizumab, an IL-6 receptor antagonist monoclonal antibody, demonstrated benefit in the reduction of inflammatory biomarkers with initially mixed results regarding mortality and frequency of intubations [5-7]. Consequently, a few major randomized clinical trials showed that the combination of an IL-6 antagonist with steroids improved survival, shortened hospital length of stay, and reduced the need for mechanical ventilation [8,9].

The optimal dosing combination of tocilizumab and corticosteroids is still unknown as there was no consistency between the dosages used in Ramiro et al., REMAP-CAP, and RECOVERY trials [8-10]. Majority of these studies dosed tocilizumab at 8 mg/kg (max 800 mg) as the standard dosing strategy [8,9,11] while other studies utilized a lower dose (max 400 mg) of tocilizumab [12,13]. At present, there is a lack of

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https://doi.org/10.1016/j.jcrc.2023.154291

Available online 10 April 2023
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Table 1
Demographics and clinical characteristics at baseline.

	Tocilizumab 400 mg ($N = 222$)	Tocilizumab > 400 mg ($N = 185$)	P-value[1]
Demographics			
Age (year)	63.0 (55.4–70.7)	62.0 (53.0–72.0)	0.595
BMI (kg/m2)	29.1 (25.5–33.0)	31.0 (28.0–35.0)	<0.001
Race/Ethnicity			0.006
White	93(41.9%)	80(43.2%)	
Black	33(14.9%)	19(10.3%)	
Hispanic	26(11.7%)	45(24.3%)	
Asian/Pacific Islander	18(8.1%)	9(4.9%)	
Other/Unknown	52(23.4%)	32(17.3%)	
Female gender	60 (27.0%)	65 (35.1%)	0.078
Comorbidities			
Hypertension	164 (73.9%)	61 (33.0%)	<0.001
DM with complication	76 (34.2%)	28 (15.1%)	<0.001
DM W/O complication	93 (41.9%)	28 (15.1%)	<0.001
CHF	18 (8.1%)	11 (5.9%)	0.399
Chronic pulmonary disease	54 (24.3%)	20 (10.8%)	<0.001
Renal Failure	54 (24.3%)	8 (4.3%)	<0.001
AIDS	3 (1.4%)	2 (1.1%)	1
Metastatic cancer	5 (2.3%)	3 (1.6%)	0.733
Solid tumor without metastasis	21 (9.5%)	14 (7.6%)	0.498
Lymphoma	3 (1.4%)	4 (2.2%)	0.707
Liver disease	38 (17.1%)	5 (2.7%)	<0.001
Medications			
Tocilizumab dose in mg (mean, [IQR])	400, (400–400)	703, (582–800)	
Corticosteroid Use (%)	222 (100%)	185 (100%)	1
Dexamethasone equivalent dose (median [IQR])	15.0(11.3–16.0)	6.4(6.0–9.3)	<0.0001
Vasopressors at time of Tocilizumab[¥]	95 (42.8%)	26 (14.1%)	<0.001
Remdesivir at time of Tocilizumab[α]	2 (0.9%)	169 (91.4%)	<0.001
Treatment Anticoagulation at time of Tocilizumab[¥]	98 (44.1%)	111 (60.0%)	0.001
Prophylaxis Anticoagulation at time of Tocilizumab[¥]	125 (56.3%)	73 (39.5%)	<0.001
Antiplatelets at time of Tocilizumab[¥]	52 (23.4%)	65 (35.1%)	0.009
Disease Severity			
ICU Admission	184 (82.9%)	113 (61.1%)	<0.001
Mechanical Ventilator at time of Tocilizumab[¥]	113 (50.9%)	30 (16.2%)	<0.001
Fio2 (%)	100(100−100)	100(95–100)	<0.001
Inflammatory Biomarkers			
D-dimer (ng/mL DDU)	2293 (755.0–4315)	376.0 (233.0–796.0)	<0.001
Ferritin (ng/mL)	1417 (862.0–2272)	1039 (573.0–1936)	0.001
CRP (mg/L)	134.9 (47.3–217.7)	114.7 (85.7–158.7)	0.437
LDH (U/L)	588.0 (467.0–820.0)	526.0 (423.0–682.0)	<0.001
WBC (10*3/uL)	10.3 (7.3–14.3)	8.6 (6.0–12.1)	0.001

[1] P-values are from the Wilcoxon rank-sum test for continuous variables and Chi-square or Fisher's exact test for categorical variables; Continuous data are presented as median (interquartile range), and categorical as frequency (percentage).

[¥] Within ±24 h of tocilizumab administration.

[α] Remdesivir was given up to 7 days prior or 24 h after tocilizumab administration.

studies comparing the two dosing strategies. In addition, a drug shortage of tocilizumab led clinicians to use either alternative therapy, such as other IL-6 inhibitors or JAK inhibitors, or to use low dose tocilizumab in contrast to a high dose. To our knowledge, there are currently no studies that have evaluated the efficacy and safety of low dose vs high dose tocilizumab in conjunction with corticosteroids for COVID-19 patients. Our study seeks to explore whether a low dose exhibits a similar benefit compared to a high dose of tocilizumab for COVID-19 patients concurrently on corticosteroids.

2. Materials and methods

2.1. Study design

We performed a retrospective, multicenter cohort study of patients admitted to the New York University (NYU) Langone Health System between March 2020 and August 2021 to evaluate the impact of fixed, low dose tocilizumab (400 mg) vs high dose tocilizumab (8 mg/kg, >400 mg) in conjunction with corticosteroids. All patients in the fixed, low dose group were treated between March 2020 and February 2021. Patients in the high dose tocilizumab group were treated between March 2021 and August 2021. The study was approved by the NYU Grossman School of Medicine Institutional Review Board.

Patients were included if they were admitted to any of the 4 hospitals within the health system (NYU Langone Medical Center [tertiary urban referral center], NYU Langone Hospital – Brooklyn [urban, low-income hospital], NYU Langone Hospital – Long Island [suburban referral center], NYU Langone Orthopedic Hospital [urban, specialty surgical hospital]), were > 18 years old, with a positive SARS-CoV-2 polymerase chain reaction (PCR) test, had a fraction of inspired oxygen (FiO_2) ≥ 70%, and received a dose of tocilizumab in conjunction with corticosteroids. Patients were excluded if they died within 24 h of the index date. As all patients received both tocilizumab and corticosteroids, the index date was defined as the date the second medication (either corticosteroids or tocilizumab) was administered and all other inclusion criteria were met. The use of FiO_2 ≥ 70% was used over the patient location or PaO2/FiO2 ratio in non-intubated patients because these are both dependent on other factors not intrinsic to the degree of hypoxia. All patients at the time received other concomitant COVID-19 medications.

Our institutional protocol has continuously changed throughout the COVID-19 pandemic. During the early phase of the COVID-19 pandemic, tocilizumab was administered as a fixed dose of 400 mg given the concern for infection. Given the limited supply, it was administered only to salvageable, non-mechanically ventilated patients while assessing the increasing rate of the inflammatory biomarkers for these patients. Patients must've had the following levels of inflammatory biomarkers to meet the criteria: ferritin >600 ng/mL, C-Reactive Protein (CRP) >100 mg/L, lactated dehydrogenase (LDH) >220 U/L. Our protocol became lenient as more supply was available and we tended to give a higher dose of 8 mg/kg adapted from the RECOVERY [9] and REMAP-CAP [14] trials. Tocilizumab was given to all severe COVID-19 patients, including those mechanically ventilated, and who also received at least two doses of dexamethasone 6 mg and had a CRP >75 mg/L. During the tocilizumab shortage and to current date, tocilizumab is restricted to those requiring mechanical ventilation.

2.2. Study variables

Data were extracted from the NYU Langone Health COVID-19 clinical database and through manual chart review. Demographic variables included age, body mass index (BMI), sex, race, Elixhauser comorbidities, and mechanical ventilation. Patients on mechanical ventilation were defined as those who were on a mechanical ventilator at the time of tocilizumab administration or were intubated within 24 h of tocilizumab administration. Laboratory variables included ferritin, C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), white blood cell (WBC) count, blood culture, Fungitell®, T2 Candida®, and cytomegalovirus (CMV) viral load. Concomitant medication use includes corticosteroids, remdesivir, therapeutic and prophylactic anticoagulation, antiplatelets, and vasopressors. Concomitant medications were collected within 24 h before and after initiation of tocilizumab except for

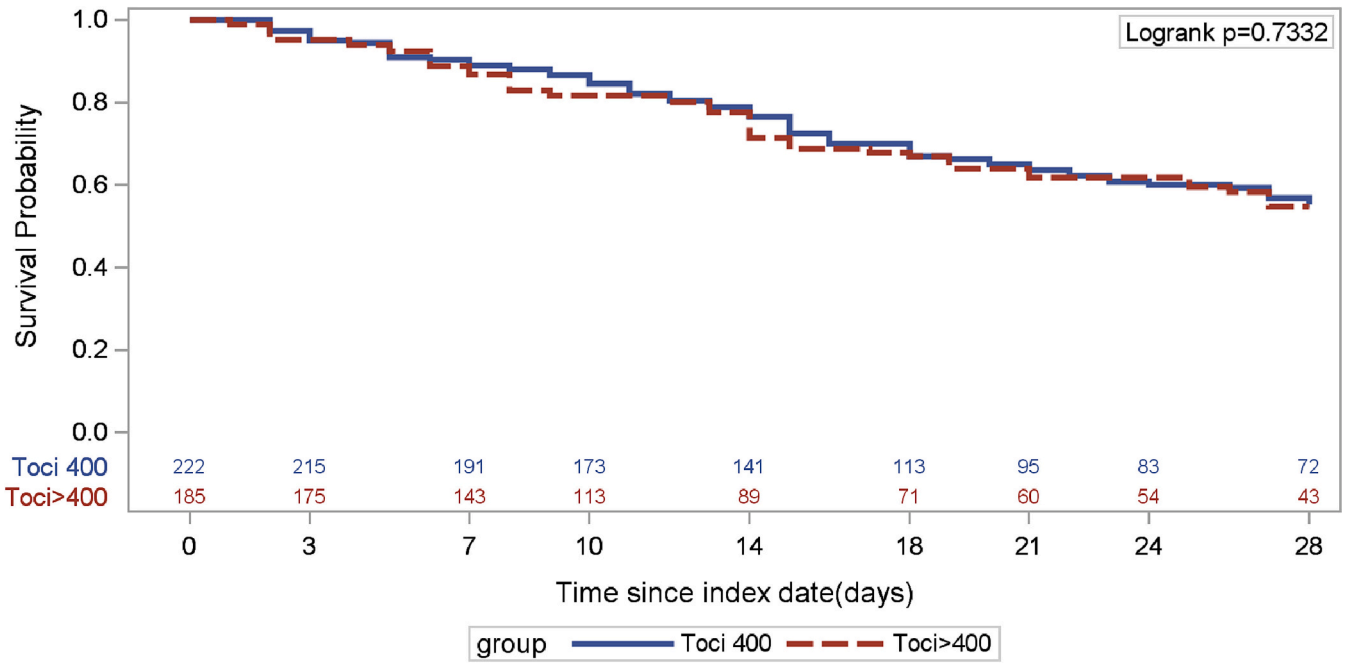

Fig. 1. 28-day mortality.
Unadjusted Hazard Ratio (95% confidence interval) for Tocilizumab 400 mg compared to Tocilizumab >400 mg group = 0.94(0.67–1.32).

remdesivir which was up to 7 days before and 24 h after tocilizumab administration.

2.3. Outcomes

Our primary outcome was 28-day mortality. If a patient was discharged alive from the hospital before 28 days, they were censored to survive. Secondary outcomes were a 14-day change in inflammatory biomarkers since the date of hospital admission and the rate of clinically apparent secondary infections. Secondary infection was analyzed for patients with a positive culture or lab result in a clinically ordered sample that was obtained at least 48 h post-administration of tocilizumab.

2.4. Statistical analysis

Baseline characteristics were categorized by group and presented using median (interquartile range [IQR]) or frequency (percentage). Wilcoxon rank-sum test was performed for continuous variables and Chi-square or Fisher's exact test for categorical variables. The primary endpoint of 28-day mortality was compared via the Kaplan-Meier method. The Cox proportional hazard model was used to compare the time from hospitalization to death. Biomarkers were log-transformed due to right-skewed distributions. The biomarker data was depicted by using percent change from the upper limit of normal (ferritin 204 ng/mL, d-dimer 309 ng/mL, CRP 5 mg/L, LDH 220 IU/L). and analyzed using mixed-effects models for repeated measures using baseline values, group, time, and two-way interaction between group and time as covariates.

The propensity score matching (PSM) technique was performed using a greedy matching algorithm to balance the groups using race, sex, BMI, treatment dose anticoagulation, prophylactic dose anticoagulation, vasopressors, antiplatelets, corticosteroid dose, a few Elixhauser comorbidities (hypertension, diabetes, chronic pulmonary disease, renal failure, AIDS, metastatic cancer, solid tumor without metastasis, lymphoma, liver disease) and dexamethasone dose equivalence. These variables were all collected at the time of tocilizumab administration and selected to match the severity of the disease and minimize the confounding effect each of these variables may have in assessing the true effect of tocilizumab in the PSM sample. The Cox proportional hazard model was used to compare the time from hospitalization to death. The exact McNemar's test was used to assess the rate of infections between groups using matched pairs. SAS 0.4 and R 4.2.1 were used to perform all analyses. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used to ensure the reporting of this retrospective, observational study [15].

3. Results

3.1. Enrollment and baseline demographics

Between March 1st, 2020, and August 1st, 2021, a total of 407 patients met our study criteria and were included in our analysis. Two hundred and twenty-two patients received fixed, low dose tocilizumab (400 mg) and 185 patients received 8 mg/kg high dose tocilizumab (> 400 mg) [Fig. S1]. Patients who received a fixed 400 mg dosing strategy were patients treated between March 2020 and February 2021 and those in the high dose group were from March 2021 to August 2021. The gender and age distribution were similar between both groups. The median BMI for both groups ranged from 29.1 kg/m^2 to 31.0 kg/m^2 ($P <$ 0.001). The average dose of tocilizumab administered was 400 mg in the low dose group and 700 mg in the high dose group. None of the patients in the fixed, low dose group received the 8 mg/kg dosing strategy as none of the patients' weight was <50 kg. No patients received a 400 mg dose from the high dose, 8 mg/kg group. Corticosteroids were administered 100% concomitantly with tocilizumab in both groups. The median dexamethasone equivalent dose of steroid used was 15 mg for the low dose group and 6.4 mg for the high dose group. In the propensity-matched groups, the median dexamethasone equivalent dose was 11 mg vs 9 mg for low dose and high dose groups respectively. Remdesivir was administered in conjunction with tocilizumab in 0.9% and 91.4% of low dose and high dose groups respectively. The low dose group was significantly more ill because a higher percentage of patients received vasopressors (42.8% vs 14.1%; $p < 0.001$), were admitted to the ICU (82.9% vs 16.1%; $p < 0.001$) and required mechanical ventilation (50.9% vs 16.2%; $p < 0.001$) compared to the high dose group (Table 1).

Table 2
Demographics and Clinical Characteristics in Propensity-Matched group.

	Tocilizumab 400 mg ($N = 56$)	Tocilizumab > 400 mg ($N = 56$)	P-value[1]
Demographics			
Age (year)	62.7 (55.7–72.0)	65.5 (59.0–76.5)	0.244
BMI (kg/m2)	32.1 (28.9–38.0)	30.5 (28.0–33.0)	0.058
Race/Ethnicity			0.58
White	23 (41.1%)	24 (42.9%)	
Black	10 (17.9%)	5 (8.9%)	
Hispanic	10 (17.9%)	10 (17.9%)	
Asian/Pacific Islander	2 (3.6%)	5 (8.9%)	
Other/Unknown	11 (19.6%)	12 (21.4%)	
Female gender	19 (33.9%)	18 (32.1%)	0.841
Comorbidities			
Hypertension	37 (66.1%)	35 (62.5%)	0.695
DM with complication	16 (28.6%)	14 (25.0%)	0.671
DM W/O complication	20 (35.7%)	16 (28.6%)	0.42
CHF	3 (5.4%)	6 (10.7%)	0.299
Chronic pulmonary disease	9 (16.1%)	11 (19.6%)	0.623
Renal Failure	7 (12.5%)	6 (10.7%)	0.769
AIDS	0 (0.0%)	1 (1.8%)	0.317
Metastatic cancer	1 (1.8%)	1 (1.8%)	1
Solid tumor without metastasis	4 (7.1%)	6 (10.7%)	0.509
Lymphoma	2 (3.6%)	2 (3.6%)	1
Liver disease	4 (7.1%)	4 (7.1%)	1
Concomitant Medications			
Corticosteroid Use (%)	56 (100%)	56 (100%)	1
Dexamethasone equivalent dose (median [IQR])	11(8–15)	9(6–14)	0.248
Vasopressors at time of Tocilizumab[¥]	16 (28.6%)	16 (28.6%)	1
Remdesivir at time of Tocilizumab[α]	2 (3.6%)	49 (87.5%)	<0.001
Treatment Anticoagulation at time of Tocilizumab[¥]	32 (57.1%)	28 (50.0%)	0.451
Prophylaxis Anticoagulation at time of Tocilizumab[¥]	24 (42.9%)	28 (50.0%)	0.451
Antiplatelets at time of Tocilizumab[¥]	18 (32.1%)	19 (33.9%)	0.841
Disease Severity			
ICU Admission	43 (76.8%)	37 (66.1%)	0.212
Mechanical Ventilator at time of Tocilizumab[¥]	25 (44.6%)	14 (25.0%)	0.03
Fio2 (%)	100 (100–100)	100 (80–100)	<0.001
Inflammatory Biomarkers[ł]			
D-dimer (ng/mL DDU)	2085 (597.0–3180)	462.0 (227.0–1753)	<0.001
Ferritin (ng/mL)	1356 (871.0–2239)	774.0 (463.0–1931)	0.023
CRP (mg/L)	135.2 (53.2–217.0)	110.7 (87.4–155.3)	0.509
LDH (U/L)	567.0 (461.0–791.0)	540.0 (424.0–636.0)	0.136
WBC (10*3/uL)	8.5 (6.3–13.6)	9.7 (7.0–13.6)	0.347

[1] P-values are from the Wilcoxon rank-sum test for continuous variables and Chi-square or Fisher's exact test for categorical variables; Continuous data are presented as median (interquartile range), and categorical as frequency (percentage).

[ł] Biomarkers has 3–12% data missing.

[¥] Within ±24 h of tocilizumab administration.

[α] Remdesivir was given up to 7 days prior or 24 h after tocilizumab administration.

3.2. Outcomes

In the Kaplan-Meier analysis of our primary endpoint using a full sample, there was no difference in 28-day mortality between groups (HR 0.94 [95% CI: 0.67–1.32]; $p = 0.733$; Fig. 1). We then performed a propensity-matched analysis for our primary endpoint—time to mortality—between groups. Among 112 matched patients (56 patients in each group) with well-balanced baseline characteristics (Table 2), the 28-day mortality using Kaplan-Meier analysis was similar between both groups (HR 0.82 [95% CI: 0.41–1.67]; $p = 0.613$; Fig. 2).

3.3. Longitudinal biomarkers

Inflammatory biomarkers (LDH, CRP, D-dimer, and ferritin) were examined over time in all groups using mixed-effects models for repeated measurements and log-transformed values. Tocilizumab was administered at a median of 3 days from the date of hospital admission. With the half-life of 11 days of tocilizumab, inflammatory biomarkers were tracked daily up to 14 days post-hospital admission. By day 14, ferritin (estimate = −0.008, $p = 0.09$), D-dimer (estimate = −0.045, $p < 0.0001$), and LDH (estimate = −0.01, $p = 0.001$) decreased while CRP (estimate = 0.18, $p < 0.0001$) increased in the low dose group compared to the high dose group (Fig. 3, Table S1). In the propensity-matched analysis group, we observed a similar trend, however, only change in CRP over time was statistically significant between the low dose and high dose group (Fig. 4, Table S2).

3.4. Secondary infections

The rate of clinically recognized secondary infections was examined between the propensity-matched groups. Positive blood cultures were identified in 14.3% of the low dose group versus 5.4% in the high dose group ($p < 0.001$). Positive Fungitell® and T2 Candida® occurred at 12.5% and 3.6% in the low dose group; 23.2% and 10.7% in the high dose group respectively ($p < 0.001$). Elevated CMV viral loads were seen in 1.8% (low dose group) vs 14.3% (high dose group) ($p < 0.001$). (Table 3.)

4. Discussion

Tocilizumab, an IL-6 receptor antagonist, has been studied for treatment in COVID-19 given its ability to mitigate systemic inflammation [3] and has been shown to lower 28-day mortality when added to corticosteroids [8,9,11]. Currently, there is limited literature investigating the efficacy, safety, and mortality of different tocilizumab dosing strategies in combination with corticosteroids. The COVIDOSE trial evaluated flat doses of 40-200 mg of tocilizumab compared to 400 mg or 8 mg/kg and identified that a low dose is sufficient to blunt both clinical and laboratory markers related to COVID-19 hyperinflammation [16]. However, this study did not include patients with concomitant corticosteroid use, which does not mimic real-life practice and does not evaluate how the dose of tocilizumab affects mortality. The MARIPOSA trial investigating the safety and efficacy of tocilizumab 4 mg/kg vs 8 mg/kg revealed no difference between groups [17]. However, this study has several major limitations. While it is a very small study, it also only consists of 22% of the patients that received corticosteroids, making it unclear whether the effect on mortality is purely due to the dose difference of tocilizumab or also influenced by the addition of corticosteroids. To better understand the dose effect of tocilizumab, we included all patients who received a low dose or high dose of tocilizumab concomitantly on corticosteroids. Our study results showed that there was a similar mortality benefit between groups.

One may wonder whether the dose of tocilizumab is influenced by the different doses of corticosteroids. Multiple studies have investigated the benefit of using a higher corticosteroid dose compared to the standard 6 mg and found that doses >6 mg do not have a better mortality benefit [18,19]. While we observed that our low dose tocilizumab group used a higher median dose of corticosteroids, our overall cohort also did not find additional mortality benefit. To further eliminate the confounding effect of the higher dose of corticosteroid in the low dose group, we propensity-matched the steroid dose in both study groups to more accurately assess the dose effect of tocilizumab and did not find additional mortality benefit. Hence, the rate of mortality in our study was not affected by the dose of corticosteroids.

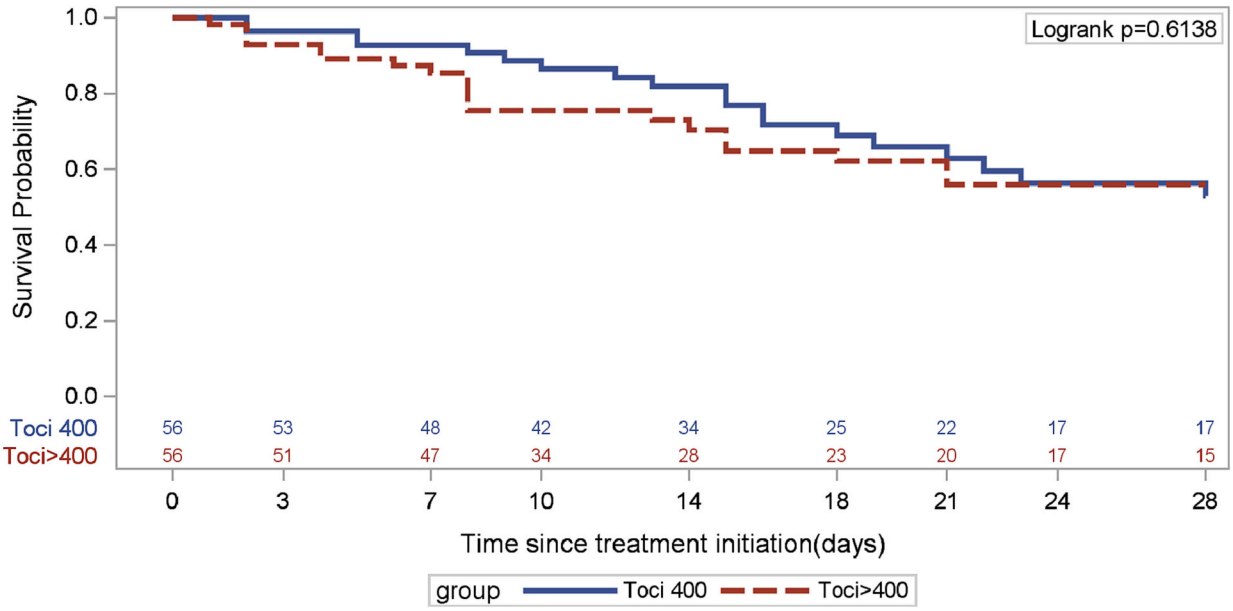

Fig. 2. 28-day mortality between propensity-matched group.
Hazard Ratio (95% confidence interval) for Tocilizumab 400 mg compared to Tocilizumab >400 mg group using stratified analysis accounting for matched sample = 0.82(0.41–1.67).

Remdesivir is part of the current standard of care in non-critically ill COVID-19 patients who are within 7 days of symptom onset. It is currently not recommended for use in mechanically ventilated patients, as data shows it has no impact on mortality in these patients [20]. In our study, 50.9% of patients in the low dose group and 16.2% in the high dose group required mechanical ventilation. Only 0.9% of patients in the low dose group received remdesivir compared to 91.4% in the high dose group. There was minimal use of remdesivir in the low dose group given the practice difference during the period. The time period with the low dose group was at the height of the initial ICU surge of the COVID-19 pandemic in New York City and the surrounding area between March 2020 and May 2020. Remdesivir was an investigational medication until it was approved as an emergency use authorization medication in May 2020. While use of remdesivir was higher in the high dose group, this did not translate into a mortality benefit. Our study echoes results from the DisCoVeRy trial in which remdesivir did not demonstrate a mortality benefit in critically ill patients on mechanical ventilation [20] and the REMDACTA trial where combination treatment with remdesivir and tocilizumab did not confirm treatment benefit in patients with severe COVID-19, [21] yet the additive combination of remdesivir to tocilizumab remains uncertain. It seems that remdesivir may not cause additional harm to patients but further studies are needed to confirm overall effect.

Cytokine storm from COVID-19 is associated with high levels of inflammatory cytokines such as ferritin, CRP, and IL-6. Initial studies have demonstrated the benefit of reduction of biomarkers specifically CRP when tocilizumab is administered [5,22]. Patients must have had a CRP level of at least 75 mg/L to receive tocilizumab in our institutional protocol. Our results agreed with previous finding showing a significant reduction in CRP but no significant difference in ferritin, d-dimer, and LDH levels when tocilizumab was administered at a median of about 3 days from the date of admission. Despite CRP being significantly reduced, this did not translate into a mortality benefit as our study did not demonstrate a statistical difference in 28-day mortality, an outcome similar to other studies.

There were initial concerns surrounding the increased risk of infection as a result of the dual immunosuppressive effect of tocilizumab and corticosteroids. However, previously reported literature has not supported this [12]. We evaluated the rate of infection between our study groups. Our results suggested a significantly increased risk of fungal and CMV infection in the high dose group. These infections may be explained by the higher concentration of the medication leading to a greater immunosuppressive effect. While we observed a higher rate of bacteremia in the low dose group, it is difficult to draw any specific conclusions as a high proportion of patients were placed on antibiotics empirically during the early phase of COVID-19 infection, meanwhile, none of our patients were placed on empiric antiviral or antifungal treatment.

The significant rise in COVID-19 cases across the country led to a shortage of tocilizumab and this has led clinicians to seek alternative options. Our study result shows similar mortality benefit while it can potentially lead to higher fungal and viral infections by utilizing the 8 mg/kg dosing strategy. By utilizing the 400 mg dose, this may translate up to 50% in cost savings. This ultimately would reserve resources to administer the medication to more patients.

Limitations of our study include the retrospective nature and lack of randomization. Retrospective studies do not allow for the investigation of causation. We used a convenience sample size that was available. Hence, the study may not have been adequately powered to detect a difference. Treatment and prevention measures of COVID-19 also have changed compared to the early vs later stages of the pandemic, which may have had an impact on our findings, such as an imbalanced use of remdesivir and COVID-19 vaccinations. The exact timing of tocilizumab with respect to COVID-19 disease onset of patients was not able to be collected. However, all patients were tested for COVID-19 upon admission where they were found to have a positive result and had an acute severity of illness requiring admission. To reduce the confounding effect of corticosteroids, propensity matching was performed to better evaluate the effect of tocilizumab after matching for steroid dose in both groups as well as concomitant medication use to ensure consistency in COVID-19 treatment.

5. Conclusion and relevance

Our study is the first study, to our knowledge, evaluating the efficacy and safety of low dose and high dose tocilizumab in patients receiving corticosteroids for the treatment of COVID-19. While many institutions have adopted the 8 mg/kg dosing strategy, the true dose of tocilizumab

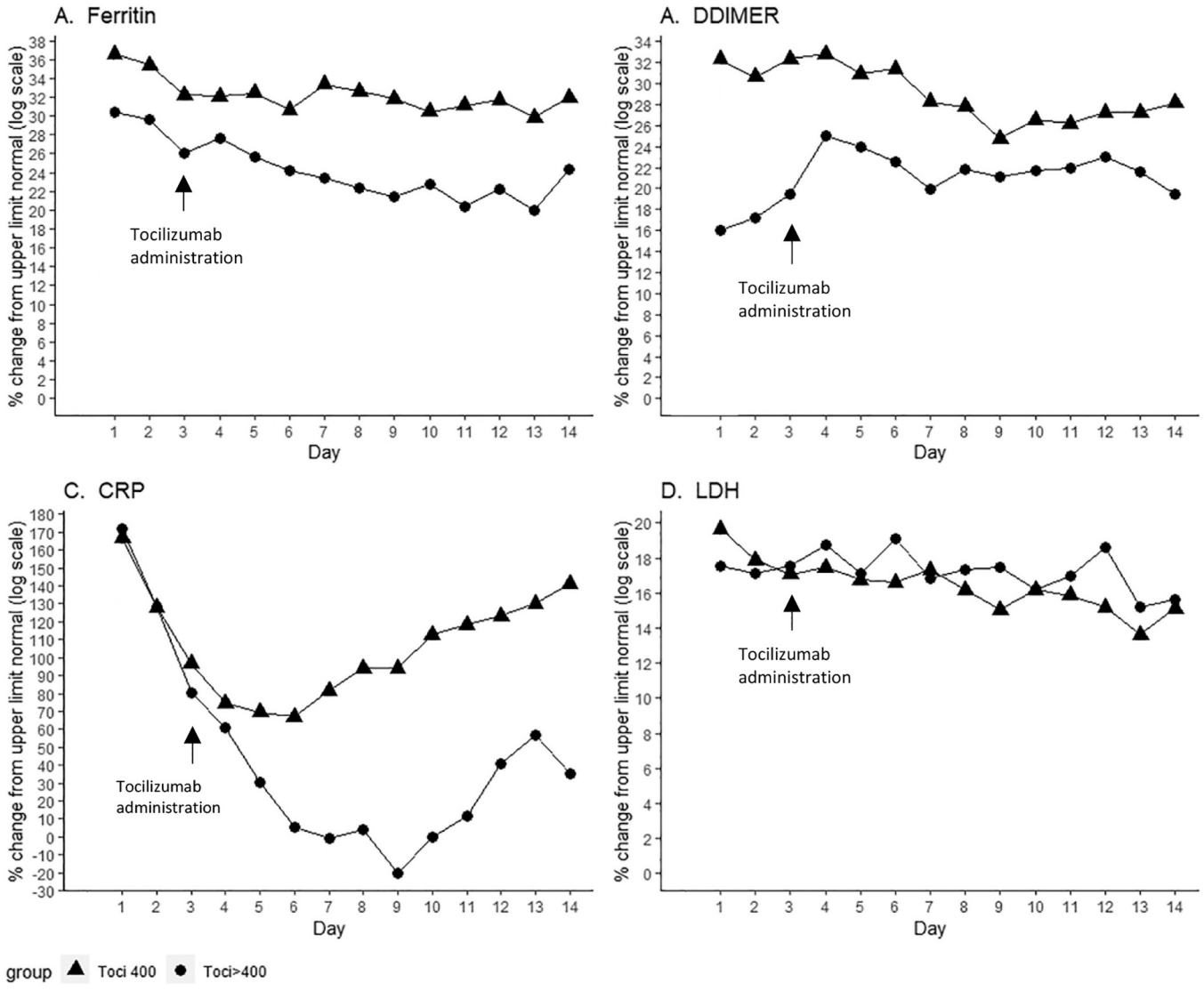

Fig. 3. 14-day change in inflammatory biomarkers.

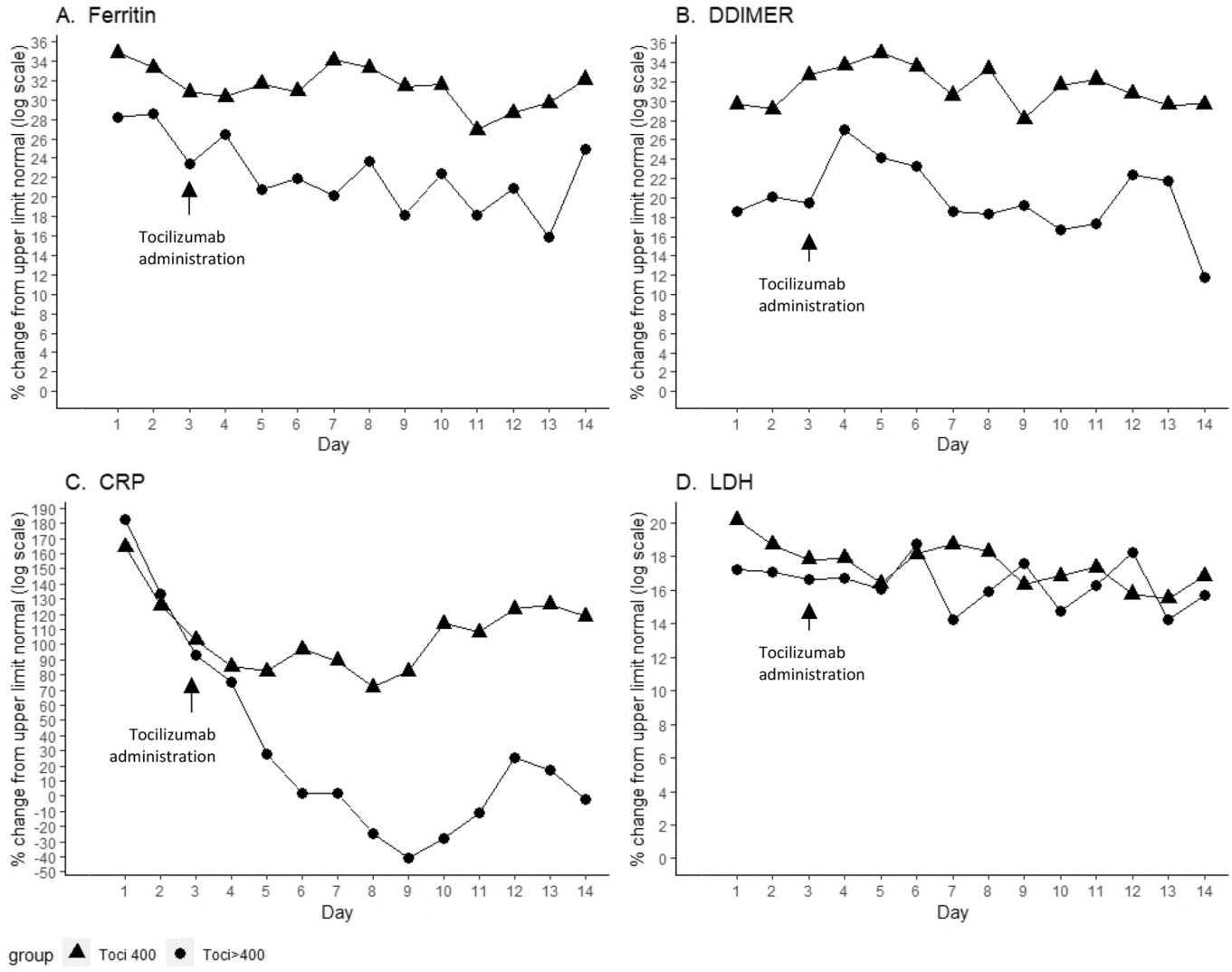

Fig. 4. 14-day change in inflammatory biomarkers in propensity-matched group.

Table 3
Secondary Infections in Propensity-Matched group.

Secondary Infections	Tocilizumab 400 (N = 56)	Tocilizumab > 400 (N = 56)	P-value[1]
Positive blood culture	8 (14.3%)	3 (5.4%)	<0.001
Fungitell	7 (12.5%)	13 (23.2%)	<0.001
T2 Candida	2 (3.6%)	6 (10.7%)	<0.001
CMV	1 (1.8%)	8 (14.3%)	<0.001

[1] P-values are from McNemar's test accounting for matched pairs; data presented as frequency (percentage).

has not been well studied. In our retrospective study, we observed that fixed, 400 mg may be as effective as 8 mg/kg and may have a lower rate of fungal and viral infections. This study provides an alternative, cost-saving option to utilize tocilizumab by reserving resources to benefit more patients.

Author's note

JC, SB, DA, and XJCC designed the study. JC, SB, DA, WKL, PS, WMW, and XJCC were clinically involved in patient care and data acquisition. SI was consulted for statistical analysis and analyzed the data. JC, SB, DA and XJCC contributed in editing the article. All authors contributed to the authorship, including review and interpretation of the data. There are no disclosures related to this research.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154291.

References

[1] Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol Jan 2021;191(1):4–17. https://doi.org/10.1016/j.ajpath.2020.08.009.
[2] Cron RQ, Caricchio R, Chatham WW. Calming the cytokine storm in COVID-19. Nat Med Oct 2021;27(10):1674–5. https://doi.org/10.1038/s41591-021-01500-9.

[3] Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med Oct 2020;26(10):1636–43. https://doi.org/10.1038/s41591-020-1051-9.
[4] Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol 2020;11:1708. https://doi.org/10.3389/fimmu.2020.01708.
[5] Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med Dec 10 2020;383(24):2333–44. https://doi.org/10.1056/NEJMoa2028836.
[6] Lewis TC, Adhikari S, Tatapudi V, et al. A propensity-matched cohort study of tocilizumab in patients with coronavirus disease 2019. Crit Care Explor Nov 2020;2(11):e0283. https://doi.org/10.1097/CCE.0000000000000283.
[7] Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol Aug 2020;2(8):e474–84. https://doi.org/10.1016/S2665-9913(20)30173-9.
[8] Investigators R-C, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med Apr 22 2021;384(16):1491–502. https://doi.org/10.1056/NEJMoa2100433.
[9] Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. May 1 2021;397(10285):1637–45. https://doi.org/10.1016/S0140-6736(21)00676-0.
[10] Ramiro S, Mostard RLM, Magro-Checa C, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. Ann Rheum Dis Sep 2020;79(9):1143–51. https://doi.org/10.1136/annrheumdis-2020-218479.
[11] Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med Jan 7 2021;384(1):20–30. https://doi.org/10.1056/NEJMoa2030340.
[12] Brosnahan SB, Chen XJC, Chung J, et al. Low-dose tocilizumab with high-dose corticosteroids in patients hospitalized for COVID-19 hypoxic respiratory failure improves mortality without increased infection risk. Ann Pharmacother Jun 28 2021. https://doi.org/10.1177/10600280211028882. 10600280211028882.
[13] Kewan T, Covut F, Al-Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID-19: a retrospective cohort study. EClinicalMedicine. Jul 2020;24:100418. https://doi.org/10.1016/j.eclinm.2020.100418.
[14] Investigators R-C, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med Feb 25 2021. https://doi.org/10.1056/NEJMoa2100433.
[15] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. Oct 20 2007;370(9596):1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X.
[16] Strohbehn GW, Heiss BL, Rouhani SJ, et al. COVIDOSE: a phase II clinical trial of low-dose tocilizumab in the treatment of noncritical COVID-19 pneumonia. Clin Pharmacol Ther Mar 2021;109(3):688–96. https://doi.org/10.1002/cpt.2117.
[17] Kumar PN, Hernández-Sánchez J, Nagel S, et al. Safety and efficacy of tocilizumab 4 or 8 mg/kg in hospitalized patients with moderate to severe COVID-19 pneumonia: a randomized clinical trial. Open Forum Infect Dis 2021. https://doi.org/10.1093/ofid/ofab608.
[18] Katz A, Altshuler D, Papadopoulos J, et al. The use of high-dose corticosteroids versus low-dose corticosteroids with and without tocilizumab in COVID-19 acute respiratory distress syndrome. Ann Pharmacother Jan 2023;57(1):5–15. https://doi.org/10.1177/10600280221094571.
[19] Group CST, Munch MW, Myatra SN, et al. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: the COVID STEROID 2 randomized trial. JAMA. Nov 9 2021;326(18):1807–17. https://doi.org/10.1001/jama.2021.18295.
[20] Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis Feb 2022;22(2):209–21. https://doi.org/10.1016/S1473-3099(21)00485-0.
[21] Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med Nov 2021;47(11):1258–70. https://doi.org/10.1007/s00134-021-06507-x.
[22] Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med Jan 1 2021;181(1):32–40. https://doi.org/10.1001/jamainternmed.2020.6820.